Exhibit C

general overview of the workup of acute and chronic diarrhea. So that was the main reason I consulted it.

Q. Do physicians in clinical practice routinely consult UpToDate for information about medications and side effects, that sort of thing?

A. I, frankly, can't really say what other doctors do. I just know that on occasion I will. If I see a patient in the hospital and I see something that I feel like I need a refresher on, I'll just go to it because it's the fastest thing I can think of. I'll either do that or just run a PubMed first.

Q. Do you consider -- do you consider UpToDate to be a reliable source of medical information?

A. You know, with the caveat that it's written, there's no peer review. It's just -- it's somewhat reliable, but it's not as reliable as a peer-reviewed randomized controlled trial. So --

Q. Have you relied on UpToDate in the course of evaluating or treating patients you

were involved with?

A. In my life? Sure.

Can I restate that? I don't know that I would use the word "rely." I rely on my clinical judgment. I may consult it to see what people are writing about current testing for what's the latest thinking about all the serologies you should consider for celiac disease or anything that might have come along, but, again, it's not a peer-reviewed source of information.

Q. In your treatment or evaluation of patients, are there times where you will look up information on UpToDate and incorporate that information into your decision-making?

A. Very rarely.

Q. Why bother looking at them? I mean, I'm not sure. You said you look at it and now it sounds like --

A. It's a quick --

Q. -- you're telling me it's like something that you wouldn't even, it's like a comic book. I can't get -- I can't get a sense from you what it is. I mean, so let's try to pin

section where I utilized it primarily was pages 13 --

Q. Fine. Where is that?

A. Pages 13 to 14.

Sorry. It's actually just through the second paragraph on page 14.

Q. The information on page 13 through the second paragraph of page 14, was that all taken from UpToDate?

A. I mean, I used UpToDate as a way for me to organize my thoughts, but some of what I wrote were -- what I wrote was just my own impression.

Q. Try to do a thorough review of UpToDate to find relevant information relevant to this case and to your opinions?

A. I didn't hear the beginning of what you said.

Q. I say, did you attempt to be thorough in finding relevant information, meaning relevant to the opinions you were going to give in this case?

A. I don't think I would say "thorough," no. I would say that I typed in

there "diarrhea evaluation" or something like that and found what they said.

Q. So in reviewing UpToDate, you didn't find the fact that it lists causes of small intestinal villous atrophy other than celiac disease, and one of those listed is medications, for example, olmesartan? You didn't see that when you went on UpToDate, did you?

MR. CHRISTIAN: Objection. Form.

THE WITNESS: I honestly can't recall because I wrote this report over a month ago, and I don't remember reading that.

BY MR. SLATER:

Q. Anywhere; correct?

A. To my recollection.

Q. I'm saying, that's not referenced anywhere in your report; right?

A. No.

Q. On page 19, you list Sleisenger and Fordtran's "Gastrointestinal and Liver Disease." What is that?

A. So that's a textbook that when I was in my training was sort of considered the

be met to establish causation; is that your understanding?

A. I don't -- I think it's more of a legal situation with the Bradford Hill criteria. I think that the more criteria you have, the stronger your case that there is an association.

Q. Okay. Here's the question. Move to strike.

Do you know in application of the Bradford Hill criteria whether it is necessary to satisfy each criteria to prove causation? Do you know?

MR. CHRISTIAN: Objection. Form.

THE WITNESS: I don't really know if you need -- so you're -- you're acting like as if every criteria is a binary result, and nothing in medicine is a binary result.

So it would be more how good is the evidence for each of those criteria, and then you would factor in everything at the end.

BY MR. SLATER:

Q. Move to strike after "I don't

be met to establish causation; is that your understanding?

A. I don't -- I think it's more of a legal situation with the Bradford Hill criteria. I think that the more criteria you have, the stronger your case that there is an association.

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So it would be more how good is the evidence for each of those criteria, and then you would factor in everything at the end.

BY MR. SLATER:

Q. Move to strike after "I don't

feel that they need to be when they have their diet when they travel and such. I've been interested in that exact question, and I think each patient has a different experience.

Q. Doctor, it's a very simple question.

Is there anything in the published literature that you can point to that says there is a dose effect with regard to gluten and celiac disease?

A. So the answer is, I don't know because I have not run a search on that because this condition that we're discussing here is not celiac disease. So it did not occur to me to look at the tens of thousands of papers about celiac disease and gluten.

Q. Do you --

A. So I'm not --

Q. -- realize that were not --

A. So I'm not prepared -- go ahead.

Q. I'm sorry. Are you still talking?

A. I'm not prepared to expound upon that detailed question.

MR. CHRISTIAN: Objection. Form.

THE WITNESS: It doesn't disprove that there could be an association.

BY MR. SLATER:

Q. The term "association" -- well, rephrase.

When one talks about an association, there are different -- rephrase.

There is a spectrum of associations from associations where you would say it's unlikely to be causal, all the way up to causal associations where you believe, yes, there's an association and it causes -- one causes the other. There's a spectrum; right?

MR. CHRISTIAN: Objection. Form.

THE WITNESS: I think that that's probably true.

BY MR. SLATER:

Q. And you agree that there is an association between olmesartan and olmesartan enteropathy as described in the literature. You just disagree that there is a causal association; correct?

A. What I would say is that there

are case series suggesting an association. However, there are multiple negative studies that I cited in my report that are higher level evidence that are different than just collecting cases where things were looked at in a more unbiased manner, and they found no association.

Q. Is there any article in the literature that you can point me to where the conclusion of the article is that there is no association between olmesartan and olmesartan enteropathy? Any article where that's the conclusion where they say there is no association?

A. So I just want to double-check what I'm about to say. So just give me a moment.

Okay. So if you look at the abstract to the Greywoode article published in 2014 out of Columbia, they looked at 2,088 patients undergoing upper endoscopy and 12,428 patients undergoing colonoscopy, and they did a multivaried analysis. Meaning they factored in different criteria which, you know, I'm not certain what every criteria were that they included.

But they found that there was no statistically significant association between olmesartan and diarrhea among those undergoing either type of procedure, and the review of the pathology reports also showed no association.

And then the concluding sentence:

"Our findings suggest that neither olmesartan nor other ARBs were associated with diarrhea among patients undergoing endoscopy."

Q. Doctor, look at the conclusion of the article.

A. That is the conclusion.

Q. Actually, don't do that. Go to the next sentence, actually, in the abstract.

Do you see the next sentence in the abstract after the one you just read?

A. Yeah, of course I do.

Q. And what does that sentence say? Read it for the record, please?

A. "The sprue-like enteropathy recently associated with olmesartan is likely a rare adverse effect and milder presentations are unlikely."

Q. So they don't conclude the association doesn't exist; right? They actually say it does exist, but it's probably rare?

A. They don't say it exists. They say "recently associated with." It doesn't mean that they're advocating it one way or the other.

Q. Doctor, look at the conclusion of the article, the last page. It says:

"Our findings suggest that the sprue-like enteropathy recently associated with olmesartan is a rare event and milder presentations causing diarrhea among substantial numbers of outpatients are unlikely."

Do you see what I just read?

A. Yes.

Q. So they're calling it a rare event; right?

A. Right.

Q. Next sentence.

Future studies should focus on the mechanisms by which olmesartan causes severe sprue-like enteropathy, and the identification of patient-related risk factors that predispose for this rare but serious outcome."

Do you see that sentence?

A. I see that sentence.

Q. Do you see that the authors actually are saying olmesartan causes severe sprue-like enteropathy? Do you see that, that's what they say --

MR. CHRISTIAN: Objection.

BY MR. SLATER:

Q. -- in their conclusion?

MR. CHRISTIAN: Objection. Form.

THE WITNESS: But that is not consistent with the findings of their study. So it doesn't make any sense that they're just referring back to other people's studies at that point.

BY MR. SLATER:

Q. Doctor, move to strike.

Do you see that that's what the sentence says?

A. I do, but I don't agree with it because that's not the conclusion of their research.

Q. Question, okay?

I'm not asking you to interpret

whether a study supports an association or not. I'm not looking to go into an interpretation. My question is very simple.

Is there any article you can point to where the authors conclude unequivocally olmesartan is not associated with either olmesartan-associated enteropathy, sprue-like enteropathy, olmesartan-induced enteropathy, however you want to name the condition? Any one where the authors make that conclusion, it did not associate it. Can you point to any article?

MR. CHRISTIAN: Objection. Form.

THE WITNESS: So, again, just because they choose to write something doesn't mean that that's what their article showed. Their article showed that there was no association when the data were considered --

BY MR. SLATER:

Q. Move to strike.

A. -- in an unbiased manner.

Q. Move to strike.

Doctor, it's a really simple question.

Is there any article you can point to where that is the explicit conclusion in the article?

A. Well, I think Greywoode does come to that conclusion.

Q. Okay. Any others?

Well, rephrase.

So you think Greywoode concludes unequivocally there's no association, even though they say that this sprue-like enteropathy recently associated is a rare event, and even though they say olmesartan causes severe sprue-like enteropathy; right? That's what you're telling the jury and the judge; right?

MR. CHRISTIAN: Objection. Form.

THE WITNESS: I'm saying that a key point to interpreting literature is to have access to the data within the paper and to be able to form your own conclusion, and my interpretation of their data is crystal clear. That there was no association in that study.

BY MR. SLATER:

Q. Okay. All right. Move to

strike.

Doctor, let's -- let's try to get on the same page because it's -- I realize what you're trying to do, but it's starting to obstruct my time.

I am not asking you to interpret the data and tell me your opinion about whether the data supports an association or not. So I would appreciate it if you would stop answering the questions as if that's what I'm asking. It's a very simple question.

Is there any article where there's an explicit conclusion by the authors that olmesartan is not associated with sprue-like enteropathy, olmesartan-associated enteropathy, or any other way you would describe that condition? Is there any article that makes that explicit conclusion; yes or no?

MR. CHRISTIAN: Objection. Form.

THE WITNESS: So my concern is that for reasons that are not clear to me that authors that are providing data, as was also seen in the Lagana study that are also completely negative, are feeling

compelled to keep referring back to these case series. So they're -- they're sort of dampening down the evidence from their own study for reasons that I don't understand.

So I don't think anybody wrote that there was no association because of the Mayo case series. However, the Lagana study is also a negative study.

BY MR. SLATER:

Q. Move to strike.

Is the answer no, there's no such article you can point to?

A. I'm not aware of any article where the only conclusion, the only thing that was stated at the end of the article was that there's no association.

Q. You're not aware of any article that actually reached the conclusion and said explicitly there is no association; correct?

MR. CHRISTIAN: Objection. Form.

THE WITNESS: How about if I read you this sentence from Lagana in the abstract:

"There were no statistically significant differences between olmesartan users with abdominal pain and controls for any single histopathological abnormality."

BY MR. SLATER:

Q. Okay. Move to strike as nonresponsive.

I'm correct that there's no article where the authors conclude there is no association; correct?

MR. CHRISTIAN: Objection. Form.

THE WITNESS: I'm going to look at another one that was negative and see what they wrote.

I guess I will say that no author felt that they could safely state that, even though their data suggested the otherwise.

BY MR. SLATER:

Q. Move to strike after the word "that."

Am I correct that there is no article you can point to where the authors

Q. So here's the question, Doctor. Focus. Here's the question.

MR. CHRISTIAN: Objection.

BY MR. SLATER:

Q. Is there any article where the authors write the words "olmesartan does not cause sprue-like enteropathy, olmesartan enteropathy" or however they might characterize that condition, where there's an explicit conclusion it doesn't cause this condition? Is there any article that says that?

A. Not --

MR. CHRISTIAN: Objection. Form.

THE WITNESS: Not to my knowledge.

BY MR. SLATER:

Q. I want to be very clear for the jury.

Do you think that olmesartan-associated enteropathy, by whatever label you want to put on it, should be evaluated as a drug allergy in determining whether there's causation or not; yes or no?

A. I'd say no. I said no.

documents look like, but my supposition is, they don't reach the level of evidence of what I would expect from a peer-reviewed paper. It would just be some -- I don't even know what it would be because I haven't seen it.

BY MR. SLATER:

Q. Really my question is pretty simple.

If there's a patient in a randomized controlled trial as I described, is it your testimony you're fine not even seeing that, it's not something that would be of any significance to you sight unseen, you don't even need to see it?

MR. CHRISTIAN: Objection. Form.

BY MR. SLATER:

Q. Is that true?

MR. CHRISTIAN: Same objection.

THE WITNESS: I don't know one. You just said "a patient." That's the singular form. I don't think one patient is worth trying to make any conclusions about causation from.

Q. So if that type of a patient -- rephrase.

So if that scenario actually exists and is known to Daiichi and their lawyers, you wouldn't even want to see it. It wouldn't even matter to you?

MR. CHRISTIAN: Objection. Form.

BY MR. SLATER:

Q. Is that your testimony?

MR. CHRISTIAN: Same objection.

THE WITNESS: I don't know whether they have controlled data on patients. I only know what's in the literature. That's what I was asked to do.

BY MR. SLATER:

Q. That's my point. If they knew about it, your testimony is you wouldn't want to see it anyway because it wouldn't be of any significance to you?

MR. CHRISTIAN: Objection. Form.

THE WITNESS: I'm really unable to answer that because, frankly speaking, I don't know what internal drug company

documents look like, but my supposition is, they don't reach the level of evidence of what I would expect from a peer-reviewed paper. It would just be some -- I don't even know what it would be because I haven't seen it.

BY MR. SLATER:

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If there's a patient in a randomized controlled trial as I described, is it your testimony you're fine not even seeing that, it's not something that would be of any significance to you sight unseen, you don't even need to see it?

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Q. Is that true?

MR. CHRISTIAN: Same objection.

THE WITNESS: I don't know one. You just said "a patient." That's the singular form. I don't think one patient is worth trying to make any conclusions about causation from.

evidence is. I would just be speculating.

BY MR. SLATER:

Q. Would you like to understand all those things so you'd understand what the company that actually sold and monitored the drug, what they actually know and think? Would you have liked to have known that?

MR. CHRISTIAN: Objection. Form.

THE WITNESS: I don't think that it's really relevant to the task that was put before me of assessing the medical literature and thinking about the science behind that because internal documents are not -- they're not peer-reviewed. I don't know anything about how they're constructed or -- or anything.

BY MR. SLATER:

Q. Your comment 19 on page 4 of your report says that -- talks about mechanism, the concept of mechanism; right?

A. Right.

Q. You do not need to know the mechanism of an association; correct?

Q. In terms of the number of patient years, Basson had a substantially higher number of patient years that were studied; correct? We've just established that?

A. Yes.

Q. The outcome of the Basson study, the data that was generated, when you weigh that, would weigh in favor of a finding of causation; correct?

A. I can't make that conclusion because they had no biopsy data they looked at. It was just hospitalization from discharge diagnosis for malabsorption. So I think that that falls short of making that conclusion.

Q. In your analysis, did you factor in the Basson study?

A. It's on page 7. At the bottom of page 7 of my report.

Q. Yeah, but now we're in your deposition where I'm asking you under oath. So my question is this:

As you sit here now offering your opinions, is the Basson data something that you are considering in forming your opinions?

So, you know, I don't have a way to put it in any context other than that.

Q. The question is: Is that a reasonable recommendation to physicians seeing patients with this type of a clinical presentation? Do you agree that's a reasonable recommendation?

A. I think that in medicine we always like to be conservative, and if we think that anything has been published, we always factor that into our consideration.

Q. If a patient comes into a gastroenterologist or a family physician, whoever it may be, who takes olmesartan and the patient has severe diarrhea, dehydration, and weight loss, based upon the medical literature as it stands now, it's a reasonable -- reasonable decision to take the patient off the olmesartan and see if the patient gets better, and if the patient does, to just switch their anti-hypertensive and avoid having to do invasive biopsies and that sort of thing.

That's a reasonable approach; correct?

MR. CHRISTIAN: Objection. Form.

THE WITNESS: So I think the reasonable approach if somebody is that sick is to stop any medication that you can find that's ever been associated with a GI distress, and then make a decision about for each of those medications whether they're needed or not or whether an alternative can be used. So there's many medications that can cause GI side effects.

BY MR. SLATER:

Q. Let's -- let's talk about a patient who is on olmesartan and is not taking any other medications that cause severe diarrhea, dehydration, and weight loss, that that's -- olmesartan is the only drug they're taking that is known to cause that spectrum.

Based on the literature that exists now, if a patient came into a doctor reporting those symptoms, it would be reasonable for the doctor to stop the olmesartan and then, if the person were to improve and then get better, to not restart the olmesartan but to go

A. Yes.

Q. Okay. I'm handing you what's been marked as Exhibit 9 to your deposition, which you indicated was your updated CV or resume, as of what date?

A. February 20, 2017.

Q. Okay. And is Exhibit 9, is that a true and correct copy of your CV?

A. Yes.

Q. Does it accurately summarize your education, training, and professional experience?

A. Yes.

Q. Will you turn to your report, which is Exhibit No. 4 in this case.

Do you have your report in front of you?

A. Yes.

Q. Turn to page 10. At the bottom of page 10, you were just asked a few questions about -- this is where the section starts on the Bradford Hill criteria; is that correct?

A. Yes.

Q. Okay. I want to ask you some questions about this criteria.

The number one criteria you list there is strength of association; correct?

A. Correct.

Q. In your evaluation of general causation in this case, did you evaluate the strength of the association that you found in the published medical literature?

A. Yes.

Q. Is that something that you do every day in your practice and in your research is evaluate strength of association?

A. Yes, I --

MR. SLATER: Objection.

BY MR. CHRISTIAN:

Q. You can still answer.

A. Yes, I do that. Whenever I'm considering any type of data that's published, whether it be something that's already published or something that I'm handling as an editor for a journal or whether I'm handling as a reviewer for an article, I need to determine what I think the quality of the associations are within that work.

Q. And you use -- utilize that methodology in your evaluation in Exhibit No. 4,

your report?

A. Yes.

MR. SLATER: Objection.

BY MR. CHRISTIAN:

Q. Or did you use that methodology in your report?

A. Yes.

Q. What is the second criteria listed on the top of page 11?

A. It should be consistency.

Q. Okay. And did you evaluate consistency in looking at the evidence in this case as it relates to olmesartan and sprue-like enteropathy?

A. Yes. In fact, that's really a striking flaw in the literature is that there is so much inconsistency in trying to define this syndrome, and I've discussed some of this in my deposition today.

Q. And in looking at the issue of consistency, is that something that you do every day in your practice and research?

A. Yes.

Q. The next item there listed is

temporality or study design suitability; is that correct?

A. Yes.

Q. And did you use the methodology of analyzing temporality or study design suitability in coming up with your opinions in this case?

A. Yes.

Q. Is that something you do every day in your practice and research?

A. Yes. We often have --

MR. SLATER: Objection.

THE WITNESS: Can I continue?

BY MR. CHRISTIAN:

Q. Yes.

A. So often in designing our human studies -- for example, I'm mentoring a senior fellow, who's joining our faculty in a new study that we're starting, and we had to very carefully think through the study design of the measurements we were going to make in patients on and off the medication for Crohn's disease. And we do the same thing when we design animal experiments.

Q. And the next item listed there is biological gradient.

Can you explain what that means?

A. So it's very important to consider the idea that if something just is cytotoxic at a low dose and you can't establish if there's a gradient, it's very hard to determine the effect in an experimental system.

In the human system, it's implicit that if somebody -- if patients were to have a deleterious effect of a medication, it seems that there should be some evidence of a dose effect; i.e. that, for example, some medications might be well tolerated at one dose, but if you increase it high enough, it could lower the seizure threshold and they could get seizures, or it could cause acute renal failure or what have you.

So that oftentimes it's very important to be able to determine if there is a gradient to an adverse effect.

Q. And, Dr. Wilson, did you analyze biological gradient in your analysis as summarized in Exhibit No. 4?

A. Yes. In fact, I indicated that there's no evidence of a biological gradient in these studies.

Q. And is evaluating biological gradient something you do every day in your practice and research?

A. Yes. When we design experiments, we often will do a dose-response of an inhibitor. We will use dose-responses of a stimulant that we're using, such as the amount of bacteria we add to cells. So we're always factoring that type of thing in.

Q. And with respect to the next category listed, specificity, do you evaluate the issue of specificity as a methodology in your everyday practice?

A. Yes, it is.

MR. SLATER: Objection.

THE WITNESS: So there's this concept of whenever you're evaluating any clinical studies, you should factor in sensitivity and specificity, but in the, you know, that's sort of assessing, for example, the merits of a certain test.

Here what we're looking at in specificity, it's something different. We're trying to see, to determine if there were to be causation, there needs to be a very specific outcome from a specific exposure.

So this idea that there could be a loose collection of responses is something that, in my opinion, lowers the quality of the evidence.

BY MR. CHRISTIAN:

Q. Did you utilize this methodology in coming up with your opinions in Exhibit No. 4?

A. I did.

Q. The next one is called biological plausibility.

What is that?

A. Well, I think that's the biggest sticking point in this entire case, which is that in order -- it's my understanding that, according to Bradford Hill criteria, in order for something to be likely to be causal, there should be a plausible biological mechanism.

And in this scenario, I gave the

example of how things like the immunosuppressive effects of HIV can be quantified by looking at a CD4 count, for example, and that can be predictive of whether people get an immunocompromised state that leads to opportunistic infection.

Here we don't have any evidence of any particular driving force because it was originally speculated that it would be TGF beta driven, a loss of TGF beta immunoregulation, but that was really an overly simplistic thought process and there are many immunoregulatory pathways and, in fact, when they looked in the Marietta paper at TGF beta, signaling they couldn't see any differences.

Q. Dr. Wilson, was part of your methodology in coming up with your opinions in Exhibit 4 analyzing biologic plausibility?

A. It was.

Q. And is that something you do in your everyday practice and research?

A. Absolutely.

Q. Number 7 is coherence.

Did you analyze coherence in

looking at the medical literature that you summarize in Exhibit No. 4?

A. So I found this one to be tough because that's supposed to be looking at the natural history of a disease, and since this is a syndrome that seems to occur in a very small number of cases, I found it very difficult to put together a coherent explanation of what this disease process is. So, for example, as I enumerated here, because of the poor quality of the evidence.

Does it include things like gastric and colonic involvement? Is that necessary to say that somebody has the syndrome? What is the role of the HLA status? What is the role of various other factors that were put forth but don't seem to be consistent between the studies?

So that further evidenced that causation is less likely because there's not coherence between the studies.

Q. As part of your methodology in coming up with your opinions in this case, did you utilize the concept of coherence?

A. I tried to see if there was any, and I didn't find much evidence of that.

Q. Is that something that you do in your everyday practice and research?

A. Yes.

Q. Number 8 is experimental evidence.

Did you use in your methodology an analysis of experimental evidence relating to sprue-like enteropathy and olmesartan?

A. I tried, but I couldn't find much. The Marietta paper, I already discussed in my report that the deficiencies there in terms of trying to provide evidence of a mechanism, and also animal data is weak. So the experimental evidence is something I considered, but it's poor.

Q. Do you, Dr. Wilson, analyze experimental evidence in your everyday practice and research?

A. I do that a lot. That's what I do every day.

Q. Okay. And number 9, reasoning by analogy.

Did you evaluate reasoning by analogy as part of your methodology in coming up with your opinions in this case?

MR. SLATER: Objection.

THE WITNESS: Yes, I did because I considered whether or not other ARBs could have the same effect, and the evidence on that is the jury is still out, so to speak, because there's a couple of scattered case reports, but there hasn't been any real effort to try and show that it's a class-specific effect. So there's not really any reasoning by analogy.

BY MR. CHRISTIAN:

Q. So in your everyday practice at Vanderbilt University and your work at the VA hospital, do you incorporate these nine different methodologies when you're trying to determine whether something is causing something else?

A. I do.

MR. SLATER: Objection.

MR. CHRISTIAN: Thank you, Dr. Wilson. That's all the questions I

Exhibit D

2013 WL 1558690
Only the Westlaw citation is currently available.
NOT FOR PUBLICATION
United States District Court,
D. New Jersey.

In re FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION.
Bernadette Glynn and Richard Glynn, Plaintiffs,
v.
Merck Sharp & Dohme Corp, Defendant.

Civil Action Nos. 11–5304, 08–08.
|
April 10, 2013.

Attorneys and Law Firms

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David J. Heubeck, Venable LLP, Baltimore, MD, Karen A. Confoy, Fox Rothschild LLP, PC, Lawrenceville, NJ, for Defendant.

OPINION

PISANO, District Judge.

***1** Plaintiffs Bernadette Glynn and Richard Glynn ("Plaintiffs") bring this lawsuit against Defendant Merck, Sharp, & Dohme Corp. ("Defendant"), which manufactures Fosamax, a drug approved by the United States Food and Drug Administration ("FDA") for the treatment and prevention of osteoporosis. This matter is part of the multi-district litigation concerning Fosamax and involves allegations that Fosamax causes atypical femur fractures ("AFFs [1]") and that it caused Plaintiff Mrs. Glynn ("Mrs.Glynn")'s femur fracture. Presently before the Court is Defendant's Omnibus *Daubert* Motion to exclude the expert testimony of Dr. Charles N. Cornell ("Dr.Cornell"), Dr. Michael J. Klein ("Dr.Klein"), Dr. David Madigan ("Dr.Madigan"), and Dr. Cheryl Blume ("Dr.Blume") as well as a motion to exclude the causation testimony of the treating physicians—Dr. Robert Busch ("Dr.Busch"), Dr. Robert Lindsay ("Dr.Lindsay"), Dr. Frederick Fletcher ("Dr.Fletcher"), and Dr. Britton Limes ("Dr.Limes") [docket # 28]. This Court heard oral argument on February 21, 2013 and April 2, 2013. For the reasons outlined below, the Motion is denied as to Drs. Cornell, Klein, Madigan, and Blume. The treating physicians' causation testimony will not be excluded if their opinions are based on their treatment and care of Mrs. Glynn.

I. DISCUSSION

Federal Rule of Evidence 702 provides that a witness

> qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if:
>
> (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
>
> (b) the testimony is based on sufficient facts or data;
>
> (c) the testimony is the product of reliable principles and methods; and
>
> (d) the expert has reliably applied the principles and methods to the facts of the case.

This Rule requires the proponent of expert testimony to show the "requisite 'qualifications, reliability, and fit' " or in other words, that "(1) the witness is qualified as an expert in a particular field; (2) the methodology applied by the witness is sufficiently reliable; and (3) the witness's testimony 'fits' the facts of the case in dispute—that is, the proffered testimony would assist the trier of fact." *Jones v. Synthes USA Sales, LLC,* 2010 WL 3311840, *4 (D.N.J. Aug.19, 2010); *see also McNamara v. Kmart Corp.,* 380 Fed. Appx. 148, 151 (3d Cir.2010); *Meadows v. Anchor Longwall & Rebuild, Inc.,* 306 Fed. Appx. 781, 788 (3d Cir.2009); *Pineda v. Ford Motor Co.,* 520 F.3d 237, 244 (3d Cir.2008); *Schneider ex rel. Estate of Schneider v. Fried,* 320 F.3d 396, 404 (3d Cir.2003).

First, the expert must be qualified; this requirement is interpreted liberally and "a broad range of knowledge, skills, and training qualify an expert as such." *In re Paoli R.R. Yard PCB Litigation,* 35 F.3d 717, 741 (3d Cir.1994).

***2** Second, "an expert's testimony is admissible so long as the process or technique the expert used in formulating the opinion is reliable." *Id.* at 742. An expert's opinion is reliable if it is "based on 'good grounds,' i.e., if it is based on the methods and procedures of science." *Id.* at 744. This inquiry requires a court to examine the "scientific validity and thus the evidentiary relevance and reliability [ ] of the principles that underlie a proposed submission" and to focus "solely on principles and methodology, not on the conclusions ... [the expert] generate[s]." *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 594–95, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993). In *Daubert*, the Supreme Court outlined several factors that a court may take into consideration in determining reliability, including whether the hypothesis can be tested, whether the methodology "has been subjected to peer review and publication," the methodology's rate of error, "the existence and maintenance of standards controlling the technique's operation," and whether there is general acceptance in the scientific community. *Id.* at 593–94. The proponent of the expert testimony must demonstrate that the opinions are reliable by a preponderance of the evidence. *In re Paoli*, 35 F.3d at 744.

Third, expert testimony "must fit the issues in the case" or in other words, "be relevant for the purposes of the case and must assist the trier of fact." *Schneider*, 320 F.3d at 404. The Court must determine "whether [the] expert testimony proffered ... is sufficiently tied to the facts of the case that it will aid the jury in resolving a factual dispute." *United States v. Schiff*, 602 F.3d 152, 173 (3d Cir.2010). This standard "is not that high" but "higher than bare relevance." *In re Paoli*, 35 F.3d at 745.

The Court's role, at a *Daubert* hearing, is to act "as a gatekeeper, preventing opinion testimony that does not meet the requirements of qualification, reliability and fit from reaching the jury." *Schneider*, 320 F.3d at 404. In keeping with its gatekeeping role, this Court will apply the *Daubert* analysis to each expert.

A. Dr. Cornell

Plaintiffs offer Dr. Cornell, an orthopedist, as an expert in causation, to establish that Fosamax causes AFFs and Mrs. Glynn's Fosamax use caused her AFF.

1. Dr. Cornell Is Qualified as an Expert

Dr. Cornell is currently a Professor of Clinical Orthopedic Surgery at Weill Cornell College of Medicine and has been the Richard Laskin Chair in Orthopedic Surgery since 2011 [docket # 102, Ex. 8, Dr. Cornell's Report ("Cornell Report") at 2]. In addition, Dr. Cornell is an attending orthopedic surgeon at the Hospital for Special Surgery in New York City and currently serves as the hospital's Director of the Department of Orthopedic Surgery. *Id.* He is a "specialist in orthopedic trauma ... and metabolic bone disease," which includes osteoporosis and osteopenia [docket # 102, Ex. 10, Dr. Cornell's Deposition ("Cornell Dep.") at 69:13–16; 71:14–17]. About 80% of all the fractures Dr. Cornell treats surgically are fractures "as a consequence of osteoporosis or osteopenia." *Id.* at 72:6–21. He has treated two patients with atypical fractures related to bisphosphonate use. Cornell Report at 3. Moreover, he has "participated in a study to determine a management strategy for the treatment of symptomatic bisphosphonate-associated incomplete atypical femoral fractures, which was peer reviewed and published in the Hospital for Special Surgery Journal." *Id.* Although Defendant argues that Dr. Cornell is not qualified because he is not trained in epidemiology and is unfamiliar with "the most basic epidemiological terms and concepts" (Db13 [2]), Dr. Cornell does not have to possess a particular subspecialty—epidemiology—to testify as an expert. *See Schneider*, 320 F.3d at 406–07 (determining that testimony was improperly excluded because an individual "was not an expert in the sub-specialty about which he opined"); *Holbrook v. Lykes Bros. S.S. Co., Inc.*, 80 F.3d 777, 783 (3d Cir.1996) (declaring that the lower court erred by requiring the expert to have a particular specialization and "exact background"); *see also Keller v. Feasterville Family Health Care Ctr.*, 557 F.Supp.2d 671, 675 (E.D.Pa.2008) (recognizing that expert testimony cannot be excluded because "the expert is without the appropriate specialization" and that "[a] certain degree of background is not required"). Because Dr. Cornell has the academic background and professional experience with osteoporosis, osteopenia, and fractures associated with those diseases, he is qualified to testify as an expert in this case. *See Schneider*, 320 F.3d at 407.

2. Dr. Cornell's Methodology Is Sufficiently Reliable

***3** Dr. Cornell formed his opinion using the Bradford Hill criteria, which are "nine factors widely used in the scientific community to assess general causation." *Gannon v. United Sates*, 292 Fed. Appx. 170, 173 (3d Cir.2008);

Cornell Dep. at 329:5–8. General causation is when "an observed association between a chemical and a disease is causal." *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F.Supp.2d 584, 592 (D.N.J.2002), *aff'd*, 68 Fed. Appx. 356 (3d Cir.2003). The nine Bradford Hill factors are: "1. Temporal Relationship, 2. Strength of the association, 3. Dose-response relationship, 4. Replication of the findings, 5. Biological plausibility (coherence with existing knowledge), 6. Consideration of alternative explanations, 7. Cessation of exposure, 8. Specificity of the association, and 9. Consistency with other knowledge." FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, at 599–600 (3d ed.2011), *available at* http://www.fjc.gov/public/pd f.nsf/lookup/SciMan3D01.pdf/$file/SciMan3D01.pdf; *see also Gannon*, 292 Fed. Appx. at 173 n. 1; *In re Avandia Mktg., Sales Practices & Products Liab. Litig.*, 2011 WL 13576, *3 (E.D.Pa. Jan.4, 2011); *Magistrini*, 180 F.Supp.2d at 592–93. "[O]ne or more of the factors may be absent even where a causal relationship exists and ... no factor is a sine qua non of causation. *Magistrini*, 180 F.Supp.2d at 593 n. 9.

Dr. Cornell used the Bradford Hill criteria to form an opinion on whether Fosamax causes AFFs. Cornell Dep. at 331:4–8; Cornell Report at 4. In applying the nine Bradford Hill factors, he reviewed Plaintiff's medical records from 1996 to present, the office notes and depositions of her treating physicians, and "past and current medical literature on the topics of osteopenia, osteoporosis and their prevention and treatment with bisphosphonate drugs including alendronate," particularly publications concerning the FIT and FLEX studies and that described the appearance of AFFs. Cornell Report at 3, 4–5. He "review[ed] the original trials, the randomized trials, that led to the approval of Fosamax for the treatment of osteoporosis, and then wanted to review many of the case reports, the case series, the summed analysis, and some of the review papers that took all of this information and put it into a more readily digestible form." Cornell Dep. at 56:13–23. Dr. Cornell attempted to "present a balanced analysis" and pointed out studies on both sides of the issue. *Id.* at 58:5–16. He concluded that Fosamax can cause AFFs and "Fosamax use was a substantial contributing factor to Mrs. Glynn's femur fracture." Cornell Report at 4. The methodology Dr. Cornell used is sufficiently reliable because the Bradford Hill criteria are "broadly accepted" in the scientific community "for evaluating causation," *Gannon*, 292 Fed. Appx. at 173 n. 1, and "are so well established in epidemiological research," *In re Avandia Mktg. ., Sales Practices & Products Liab. Litig.*, 2011 WL 13576, at *3.

***4** Defendant, however, argues that Plaintiffs do not explain the scientific methodology used by Dr. Cornell or show that his methodology is sufficiently reliable. Instead, Defendant asserts that Dr. Cornell's "weight-of-the-evidence" methodology just lists some studies, only some of which support causation, and concludes that the weight of the evidence shows that Fosamax causes AFFs. Defendant explains that this method is inadequate because Dr. Cornell does not discuss how these studies establish causation or why certain studies outweigh others that do not find causation. Additionally, Defendant points out that Dr. Cornell has not done an evaluation of possible biases or confounding factors found in the studies. Because Dr. Cornell does not show that his methodology is sufficiently reliable to show general causation, Defendant argues that he cannot establish specific causation—that Mrs. Glynn's Fosamax use caused her AFF. Defendant explains that the Bradford Hill criteria do not apply to specific causation, and Dr. Cornell's differential diagnosis was unreliable because he did not rule out the possibility that other things could have caused Mrs. Glynn's fracture.

Defendant is free to address these issues on cross-examination, but Defendant's concerns do not prohibit Dr. Cornell from testifying as an expert because he is qualified and the methodology he used is sufficiently reliable. *See Milward v. Acuity Specialty Products Group, Inc.*, 639 F.3d 11, 15 (1st Cir.2011), *cert. denied*, — U.S. ——, 132 S.Ct. 1002, 181 L.Ed.2d 734 (2012) (stating "*Daubert* does not require that a party who proffers expert testimony carry the burden of proving to the judge that the expert's assessment of the situation is correct"; instead, the "proponent of the evidence must show only that 'the expert's conclusion has been arrived at in a scientifically sound and methodologically reliable fashion.' ").

Regarding Dr. Cornell's specific causation opinion that Fosamax caused Mrs. Glynn's femur fracture, he applied the differential diagnosis method, which is "a technique that involves assessing causation with respect to a particular individual." *Kannankeril v. Terminix Int'l, Inc.*, 128 F.3d 802, 807 (3d Cir.1997). It "is a process by which a physician rules out alternative causes through review of a patient's medical histories and

records, physical examination of the patient, laboratory testing, study of relevant medical literature, and other techniques." *In re Diet Drugs (Phentermine/Fenfluramine/Dexfenfluramine) Products Liab. Litig.*, 890 F.Supp.2d 552, 561 (E.D.Pa.2012). The "technique is generally accepted in the medical community." *Id.*

Here, Dr. Cornell applied the differential diagnosis method by examining Mrs. Glynn's past medical history and conducting his own examination of her on September 26, 2012, after which he concluded that "[t]o a reasonable degree of medical certainty, Mrs. Glynn suffered a nontraumatic [AFF] in the setting of seven years of full dose Fosamax and alendronate therapy." Cornell Report at 34–36. Dr. Cornell reviewed radiographs taken on April 17, 2009 to evaluate the fracture and reviewed follow-up X-rays, hospital records, rehabilitation records, orthopedics records, prescription records from pharmacies, and deposition transcripts, among other things, in forming his opinion [docket # 109, Ex. 78, Appendix B to Cornell Report]. He ruled out possible alternative causes of Mrs. Glynn's AFF. Cornell Report at 38–40, 42–43, 45–46. Dr. Cornell did not have to "rule out every possible alternative cause of" Mrs. Glynn's AFF; instead, only "[o]bvious alternative causes need to be ruled out." *Heller v. Shaw Indus., Inc.*, 167 F.3d 146, 156 (3d Cir.1999). Thus, Dr. Cornell applied the differential diagnosis method in arriving at his conclusion that Mrs. Glynn's Fosamax use was a substantial contributing factor to her AFF.

***5** Therefore, the methodology used by Dr. Cornell in arriving at both his general and specific causation opinions is sufficiently reliable. Both the Bradford Hill criteria and differential diagnosis are widely used and accepted in the scientific community to arrive at causation opinions.

3. Dr. Cornell's Testimony Fits the Facts of the Case

Finally, Dr. Cornell's testimony fits the facts of the dispute and will assist the trier of fact because Plaintiffs seek to show that Mrs. Glynn's AFF was caused by her Fosamax use and Dr. Cornell not only opines that AFFs are caused by long term bisphosphonate use, like Fosamax, but also that Mrs. Glynn's Fosamax use was a "substantial contributing factor to her" AFF. *See* Cornell Report at p. 22, 47. Consequently, Dr. Cornell's proffered testimony will assist the trier of fact in determining whether Fosamax caused Mrs. Glynn's AFF.

Because Dr. Cornell is qualified, used a methodology that is sufficiently reliable, and his opinion fits the facts of a case, his expert testimony is admissible under *Daubert*.

B. Dr. Klein

Plaintiffs asked Dr. Klein, a pathologist, to offer his opinion on whether Fosamax use causes AFFs and the "mechanism by which those fractures are precipitated" [docket # 103, Ex. 11, Dr. Klein's Report ("Klein Report") at 2].

1. Dr. Klein Is Qualified as an Expert

Dr. Klein is currently the Director of Pathology and Laboratory Medicine at the Hospital for Special Surgery where he has "direct clinical responsibilities for patients ...." *Id.* at 3–4. He also has "direct clinical responsibilities ... as a consultant at Memorial Sloan–Kettering Cancer Center, and as an outside counsel for leading pathology laboratories at major hospitals and institutions around the country." *Id.* at 4. Dr. Klein has reviewed the pathology for at least four patients with AFFs [docket # 105, Ex. 37, Dr. Klein's Deposition ("Klein Dep.") at 41:4–12]. Dr. Klein is currently a Professor of Pathology and Laboratory Medicine at Weill Cornell Medical College. Klein Report at 3. He is involved with several publications, including as the lead author and editor of *Non-neoplastic Diseases of Bones and Joints,* the only peer-reviewed, comprehensive textbook on the issue, and as a member of the editorial boards of *Human Pathology, Skeletal Radiology, Advances in Anatomical Pathology,* and *HSS Journal. Id.* Dr. Klein is the Consultant Editor of Research for *The Journal of Bone and Joint Surgery (American)* and has authored or co-authored more than 180 articles, most of which relate to bone pathology. *Id.* Therefore, Dr. Klein possesses "a broad range of knowledge, skills, and training" to qualify him as an expert in pathology. *In re Paoli*, 35 F.3d at 741.

2. Dr. Klein's Methodology Is Sufficiently Reliable

Like Dr. Cornell, Dr. Klein used the Bradford Hill criteria to form his opinion. Klein Report at 2. As discussed above, the Bradford Hill methodology is sufficiently reliable because it is "widely used in the scientific community to assess general causation." *Gannon*, 292 Fed. Appx. at 173. In applying the nine Bradford Hill criteria, Dr. Klein reviewed human and animal studies

and studies performed by Defendant to form his opinion. *See* Klein Report at19–38. The studies revealed a strong association between bisphosphonates, like Fosamax, and microdamage in the bones as well as decreased bone toughness. *See id.* at 20, 25–30, 32. In addition, Dr. Klein noted a strong association between delayed fracture healing, due to altered bone quality, in patients and animals taking bisphosphonates. *Id.* at 23–24, 29. These findings were replicated in several studies discussed in Dr. Klein's report. Moreover, Dr. Klein cited one study which recognized the *"duration*-dependent, as well as dose-dependent, effect bisphosphonates have on the skeleton." *Id.* at 27. Another study mentioned in Dr. Klein's report noted that the "cessation of bisphosphonate treatment may be prudent for women on therapy who sustain a nonvertebral fracture." *Id.* at 30. Thus, Dr. Klein applied the Bradford Hill criteria, including the strength of association, replication of findings, dose-response relationship, and cessation of exposure factors.

***6** Based on his review of the studies, Dr. Klein concluded that "alendronate significantly alters the cellular properties of bisphosphonate-treated bone." *Id.* at 38. AFFs are not

> attributed to low bone mass or osteoporosis alone, indicative of bone that has fundamentally compromised bone microstructure. Unless a damaging force exerts tension across the entire cortex, the laws of physics and biomechanics as applied to bone further support the conclusion that bone quality and microstructure must be fundamentally compromised for a transverse fracture in a hollow cylinder[, like the femur,] to follow.
>
> [*Id.*]

Thus, Dr. Klein opined that there is a causal relationship between Fosamax and AFFs. *Id.* at 2. He used a sufficiently reliable methodology, the Bradford Hill criteria, in forming this opinion.

Defendant, however, argues that the Bradford Hill criteria apply to epidemiology studies, which Dr. Klein's report does not discuss. Defendant contends that Dr. Klein has not provided support for the proposition that a general causation conclusion can be established using the Bradford Hill criteria and human or animal biopsy data. In addition, Defendant asserts that if Dr. Klein discussed epidemiology studies in his report, he did not demonstrate that he is qualified to interpret that evidence because he has no expertise in epidemiology and does not understand the most basic epidemiology terms. Moreover, Defendant points out that Dr. Klein conceded that the mechanism regarding how bisphosphonates cause AFFs has not been established and that the theories Dr. Klein uses to support his conclusion about mechanism—microdamage, decrease in tissue heterogeneity, bone brittleness, and delayed healing—have not been proved with human data.

Yet, Dr. Klein has properly applied the Bradford Hill criteria to epidemiological studies. Epidemiological studies include randomized trials in which one group is exposed to an agent, such as Fosamax, and another group is not, and the effect of the agent or lack thereof is observed. FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE at 555–56. Here, Dr. Klein examined randomized trials, such as Dempster et al., Boskey et al., and Donnelly et al.; in each of these studies, some women were given alendronate or another bisphosphonate and others were not. Klein Report at 20–21. Moreover, the Federal Judicial Center's Reference Manual on Scientific Evidence states that "toxicology models based on live animal studies ... may be used to determine toxicity in humans" in addition to observational epidemiology. FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, at 563.

For his testimony to be admissible, Dr. Klein is not required to show that the mechanism has been definitely established. Instead, he just needs to show that the methodology he used to arrive at his opinion is sufficiently reliable. *See Milward,* 639 F.3d at 15 (stating *"Daubert* does not require that a party who proffers expert testimony carry the burden of proving to the judge that the expert's assessment of the situation is correct"; instead, the "proponent of the evidence must show only that 'the expert's conclusion has been arrived at in a scientifically sound and methodologically reliable fashion.' "). Dr. Klein arrived at his opinion on the mechanism by examining several studies and using a scientific method that is sufficiently reliable.

3. Dr. Klein's Testimony Fits the Facts of the Case

***7** Lastly, Dr. Klein's testimony fits the facts of the dispute and will assist the trier of fact. *See Jones,* 2010 WL 3311840, at *4. Through Dr. Klein's testimony, Plaintiffs seek to show that Fosamax causes AFFs and

the mechanism by which this happens. *See* Klein Report at 2. Dr. Klein opines that Fosamax causes AFFs and discusses several ways this happens—microdamage, abnormal osteoclasts, altered bone quality, and delayed fracture healing. Thus, Dr. Klein's testimony will assist the trier of fact in determining whether Fosamax causes AFFs, the ways in which this happens, and ultimately, his testimony will aid the jury in deciding whether Mrs. Glynn's Fosamax use caused her AFF.

C. Dr. Madigan

Plaintiffs asked Dr. Madigan, a statistician, to give his opinion regarding "whether a signal of problematic oversuppression of bone turnover and associated [AFF] ... existed for Fosamax, using industry standard pharmacovigilance techniques and data sources, and the adverse event terms selected by Merck to internally evaluate the same" and "assess the strength of that signal, if any, in comparison to the signal, if any, for such events in other products indicated for the prevention and treatment of osteoporosis" [docket # 33, Ex. 30, Dr. Madigan's Report ("Madigan Report") at ¶ 5].

1. Dr. Madigan Is Qualified as an Expert

Dr. Madigan is Professor and Chair of Statistics at Columbia University. *Id.* at ¶ 1. He is an elected Fellow of the Institute of Mathematical Statistics and the American Statistical Association, and from 1995 to 2005 was the 36th most cited mathematician worldwide. *Id.* In 2010, he completed a term as Editor of the journal *Statistical Science. Id.* Dr. Madigan has consulted for companies such as Novartis, Pfizer, and Sanofi–Aventis on several issues, "many related to drug safety." *Id.* at ¶ 2. He has statistical experience with clinical trials and has published more than 100 technical papers on many topics, including pharmacovigilance [3]. *Id.*

Within the last few years, drug safety "with a focus on the development and application of statistical methods for pharmacovigilance" has been "one of [Dr. Madigan's] significant research interests ...." *Id.* at ¶ 3. He has published work in several journals, including *Drug Safety, Pharmacoepidemiology and Drug Safety,* and *Epidemiology. Id.* Dr. Madigan is an investigator in the Mini–Sentinel project, which is "a pilot project sponsored by the FDA to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products." *Id.* He is the "methods lead for the Observational Medical Outcomes Partnership, a public-private partnership between the FDA and the pharmaceutical industry, which addresses "research methods that are feasible and useful to analyze existing healthcare databases to identify and evaluate safety and benefit issues of drugs already on the market." *Id.* Dr. Madigan is a member of the FDA's Drug Safety and Risk Management Committee, which "advises the FDA Commissioner on risk management, risk communication, and quantitative evaluation of spontaneous reports for drugs for human use and for any other product for which the FDA has regulatory responsibility." *Id.* Dr. Madigan is qualified as an expert because he has "a broad range of knowledge, skills, and training [to] qualify ... [him] as such." *In re Paoli,* 35 F.3d at 741. Defendant does not dispute Dr. Madigan's qualifications.

2. Dr. Madigan's Methodology Is Sufficiently Reliable

***8** Dr. Madigan examined the FDA's Adverse Event Reporting System ("AERS") database for a "possible association between Fosamax and a series of ... terms selected by Merck to evaluate oversuppression of bone turnover and associated" AFFs. Madigan Report at ¶ 25. The terms were: bone development abnormal, bone disorder, bone formation decreased, fracture delayed union, fracture malunion, fracture nonunion, low turnover osteopathy, pathological fracture, stress fracture, fracture, and femur fracture. *Id.* at ¶ 26. Dr. Madigan used "two industry-standard signal detection algorithms ... to assess whether or not Fosamax presented a safety signal" indicating oversuppression of bone turnover or AFFs. *Id.* at ¶ 25. The QScan pharmacovigilance software computed the statistics. *Id.* at ¶ 27. Dr. Madigan then compared the Fosamax signals to other oral bisphosphonates and a non-bisphosphonate used for the treatment and prevention of osteoporosis. *Id.* at ¶ 25. After reviewing the data, Dr. Madigan opined that

> industry standard pharmacovigilance techniques and datasources reveal the presence of a clear signal for oversuppression of bone turnover and associated atypical femur fracture events utilizing the terms selected by Merck for such analysis. By standard metrics of "signal" detection, the signal is strong, consistent, and not ambiguous. Of perhaps greater concern, the signal was striking in comparison to that for other drugs indicated for the prevention and treatment of osteoporosis. As early as 2001–2002, the

> spontaneous report data for Fosamax provide signals for a number of indicators of suppression of bone turnover. For the comparator drugs, such signals either never appear or appear years later.
>
> [*Id.* at ¶ 36.]

This opinion is admissible because it is based on a method that is sufficiently reliable. *See Jones,* 2010 WL 3311840, at *4. Two factors that a court may take into consideration in determining reliability is whether the methodology has been subjected to peer review and publication and whether there is general acceptance in the scientific community. *Daubert,* 509 U.S. at 593–94. Here, Dr. Madigan's method, data mining in pharmacovigilance, is generally accepted in the scientific community and has "become routine both in the pharmaceutical industry and amongst regulators worldwide." Madigan Report at ¶ 8. In fact, "[p]harmaceutical companies, health authorities, and drug monitoring centers use SRS databases for global screening for signals of new adverse events or changes in the frequency, character, or severity of existing adverse events (AEs) after regulatory authorization for use in clinical practice." *Id.* at ¶ 9. "SRS systems provide the primary data for day-to-day drug safety surveillance by regulators and manufacturers worldwide." *Id.* at ¶ 14. In addition, the QScan software Dr. Madigan used in formulating his opinion is generally accepted by the scientific community because it "has been in widespread use for over 10 years and has been validated extensively." *Id.* at ¶ 28. Moreover, "[m]any peer-reviewed publications report results derived from QScan." *Id.* Thus, Dr. Madigan's methodology is sufficiently reliable.

***9** Although Defendant argues that Dr. Madigan's methodology is unreliable because he did not review the substance of the adverse event reports to see if they actually involve AFFs or oversuppression of bone turnover, this argument is inappropriate on a *Daubert* motion. Dr. Madigan's testimony will be subject to cross-examination, and the credibility of his opinion will be ultimately determined through the adversarial process. Dr. Madigan's methodology is sufficiently reliable because it is generally accepted in the scientific community, and therefore, Plaintiffs have satisfied the second prong of *Daubert.*

3. Dr. Madigan's Testimony Fits the Facts of the Case

Lastly, Dr. Madigan's testimony fits the facts of the case and will assist the trier of fact because it is related to Plaintiffs' failure to warn claim. *See Jones,* 2010 WL 3311840, at *4. A failure to warn claim requires a plaintiff to show "(1) that a manufacturer has a duty to warn (2) against dangers resulting from foreseeable uses about which it knew or should have known and (3) that failure to do so was the proximate cause of the harm." *In re Fosamax Prods. Liab. Litig.,* 2013 WL 76140, *3 (S.D.N.Y. Jan.7, 2013). Dr. Madigan's testimony fits the facts of this case because he opines that "[a]s early as 2001–2002, the spontaneous report data for Fosamax provide[d] signals for a number of indicators of suppression of bone turnover," meaning Defendant knew or should have known that Fosamax caused certain dangers in 2001–2002, thus imposing on Defendant a duty to warn of those dangers. Madigan Report at ¶ 36.

Defendant, however, argues that Dr. Madigan's testimony does not fit the facts of the case because it is irrelevant since there is no reasonable standard of care that would have required Defendant to conduct data mining. This is also a matter best left to the credibility determination of the jury.

As a result, Dr. Madigan's expert testimony is admissible under *Daubert* because he is qualified, he used a sufficiently reliable methodology, and his opinion fits the facts of the case.

D. Dr. Blume

Dr. Blume is offered as an expert in pharmacovigilance and FDA regulation. Plaintiffs offer the testimony of Dr. Blume to: (1) "address the timeliness and completeness of the efforts undertaken by [Defendant] ... to fully inform prescribers and patients of the increasingly adverse benefit risk assessments associated with long-term Fosamax use in postmenopausal women"; (2) "evaluate the negative consequences of protracted bone oversuppression," including AFFs, in people receiving Fosamax; and (3) "to consider the pharmacovigilance activities undertaken by [Defendant] to evaluate the noted adverse events during the relevant time periods" [docket # 119, Ex. 33, Dr. Blume's Report ("Blume Report") at ¶ 6].

1. Dr. Blume is Qualified as an Expert

Dr. Blume received her Ph.D. in Pharmacology and Toxicology from the West Virginia University

Medical Center and is currently the President of Pharmaceutical Development Group, Inc. (PDG), "a consulting firm ... specializing in pharmaceutical development and registration activities." *Id.* at ¶ 1. In this role, she "has been responsible for preclinical and clinical (Phases I–IV) programs associated with pharmaceutical product development and the securing of pre-marketing approvals" for many drugs before the FDA. *Id.* at ¶ 2. Additionally, Dr. Blume has directed "all phases of interactions with [the] FDA relating to the prosecution of New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), Supplements to New Drug Applications (sNDAs), and the associated approval procedures," including "the collection and evaluation of postmarketing adverse medical events, the preparation of updated product labeling, and the dissemination of accurate, complete and timely product-related information to health care providers." *Id.* at ¶ 3. She was responsible for "regulatory review of promotional and education materials for both brand-name and generic drug products." *Id.* Dr. Blume's responsibilities include the "design, execution, and interpretation of pivotal safety-related trials and the development and implementation of pharmacovigilance procedures intended to detect new safety signals and track the evolution of previously identified signals." *Id.* at ¶ 4. She has directed "all phases of interactions with the FDA relating to post-approval labeling procedures regarding changes to safety-related information based upon postmarketing signal tracking and pharmacovigilance efforts," including "collection and evaluation of postmarketing adverse medical events, review and interpretation of the results of postmarketing clinical studies, the preparation of updated product labeling and other communication tools, and the dissemination of new product information to health care providers, patients, and consumers." *Id.* at ¶ 5. Dr. Blume possesses the knowledge, skills, and training necessary to qualify her as an expert. *See In re Paoli,* 35 F.3d at 741. Defendant does not dispute Dr. Blume's qualifications.

2. Dr. Blume's Methodology Is Sufficiently Reliable

***10** Dr. Blume reviewed published studies (Blume Report at ¶¶ 57–74), Merck's Period Safety Update Reports (*id.* at ¶ 75), Dr. Madigan's report (*id.* at ¶¶ 76–78), Merck's Worldwide Adverse Experience System ("WAES") (*id.* at ¶ 79), and epidemiological studies (*id.* at ¶¶ 82–90). *See also* docket # 119, Ex. 5, Dr. Blume's Deposition ("Blume Dep.") at 148:9–18; 338:9–20 (stating that she looked at the WAES database, literature reports, epidemiological studies, the AERS database, and Dr. Madigan's report). She discussed the "specific regulatory procedures and regulations" pharmaceutical manufacturers have to comply with, including procedures and regulations related to FDA approval, labeling, postmarketing surveillance, and reporting requirements. *Id.* at ¶¶ 11–34. Dr. Blume evaluated all of this information using "her years of experience" in "the industry," *see In re Viagra Products Liability Litigation,* 658 F.Supp.2d 950, 962 (D.Minn.2009), and opined that

> the scientific literature, Merck's internal adverse event database, the AERS database, and epidemiology analyses confirmed the increasingly adverse risk-benefit profile related to long-term Fosamax use in the indicated populations. However, Merck permitted their labeling and other prescriber information to remain static with respect to both the deteriorating risk-benefit assessment and the escalation in ... [AFF] reports. Such omissions do not comply with the regulatory and industry standards of responsible pharmaceutical companies .... Merck also should have undertaken timely and adequate studies to more clearly elucidate the risks of Fosamax use in the various indicated populations. Finally, Merck should have disseminated Dear Healthcare Professional Letters to advise prescribers and their patients of the escalating safety and efficacy concerns. Merck's omissions have likely resulted in the exposure of numerous patient populations to unnecessary risks associated with the initiation and ongoing treatment with Fosamax.
>
> [Blume Report at ¶ 110.]

Dr. Blume states that "[b]y the early 2000's, it was known that ... [AFFs] were clinically significant events ...." *Id.* at ¶ 109. Dr. Blume opines that Defendant should have changed the Fosamax label "to include escalating warning and precautionary risk information related to" AFFs. *Id.* Instead, Dr. Blume notes that Defendant "did not identify these fractures in the labeling until 2009" even though it received reports that AFFs were "associated with Fosamax use as early as 2002." *Id.* at ¶¶ 31, 82.

Defendant argues that the Court should exclude Dr. Blume's opinions on: (1) the legal requirements governing pharmaceutical manufacturers and Defendant's compliance with those requirements; (2) Defendant waiting too long to add information about femur fractures

to the Adverse Reactions section of the label; (3) Defendant failing to add a warning or precaution about femur fractures to the Fosamax label before 2009; (4) Defendant's failure to timely investigate a potential link between Fosamax and AFF; (5) Defendant's alleged motives or state of mind; (6) the causation or mechanism of AFF; and (7) the drug Evista is safer than Fosamax. Yet, because *Daubert* concerns the narrow issue of whether expert testimony is admissible, this is not the appropriate time for Defendant to request that the Court preclude Dr. Blume from testifying about certain topics. Defendant may question Dr. Blume's opinions or methodology on cross-examination. *See Milward,* 639 F.3d at 15 (stating "[s]o long as an expert's scientific testimony rests upon "good grounds," based on what is known, ..., it should be tested by the adversarial process, rather than excluded").

***11** Despite Defendant's issues with Dr. Blume's opinions, Plaintiffs have satisfied the second prong of *Daubert* because Dr. Blume's methodology is sufficiently reliable.

3. Dr. Blume's Testimony Fits the Facts of the Case

Dr. Blume's testimony fits the facts of the case because she opines that it was known in the early 2000's that AFFs were associated with Fosamax use. *See* Blume Report at ¶¶ 31, 82. Dr. Blume's testimony is relevant and will assist the trier of fact in deciding Plaintiffs' failure to warn claim because Dr. Blume's opinion is relevant to whether and when Defendant knew or should have known that AFFs were associated with Fosamax and therefore, when Defendant should have sought a label change. *See Schneider,* 320 F.3d at 404 (recognizing that expert testimony must "be relevant for the purposes of the case and must assist the trier of fact").

E. Treating Physicians

Defendant argues that the Court should preclude causation testimony from Plaintiffs' treating physicians —Drs. Busch, Lindsay, Fletcher, and Limes—because: (1) Plaintiffs have not provided Rule 26 disclosures for any of the treating physicians; and (2) none of the treating physicians are able to offer a reliable causation opinion to a reasonable degree of medical certainty. Plaintiffs, however, assert that they do not intend to elicit expert testimony from the treating physicians; instead, the treating physicians will testify about Mrs. Glynn's care and treatment, which does not require Rule 26 disclosures.

Treating "physicians are not required to submit expert reports when testifying based on their examination, diagnosis and treatment of a patient." *Patterson v. Howard,* 2010 WL 1050052, *4 (D.N.J. Mar.18, 2010). Federal Rule of Civil Procedure 26(a)(2)(B) requires a witness to submit a written report only "if the witness is one retained or specially employed to provide expert testimony in the case or one whose duties as the party's employee regularly involve giving expert testimony." A "treating physician is not necessarily retained or specially employed to provide expert testimony simply because he or she proffers on causation and prognosis" because "doctors may need to determine the cause of an injury in order to treat it." *Pease v. Lycoming Engines,* 2012 WL 162551, *12 (M.D.Pa. Jan.19, 2012). In order to "determine whether a party retained or specially employed a treating physician to provide expert testimony," the Court must examine "whether the treating physician acquired his opinion as to the cause of ... plaintiff's injuries directly through his treatment of the plaintiff." *Id.* (internal quotation omitted). As a result, treating physicians are not required to submit expert reports "if they form their opinion on causation or prognosis as part of the ordinary care of a patient." *Id.*

Therefore, the testimony of Drs. Busch, Lindsay, Fletcher, and Limes is appropriate if it is based on their care and treatment of Mrs. Glynn. This Court will not allow, however, any expert testimony on causation from these physicians.

II. CONCLUSION

***12** For the reasons outlined above, this Court denies Defendant's *Daubert* Motion as to Drs. Cornell, Klein, Madigan, and Blume. An appropriate Order accompanies this Opinion.

All Citations

Not Reported in F.Supp.2d, 2013 WL 1558690, 91 Fed. R. Evid. Serv. 106

Footnotes

1 The abbreviation of atypical femur fracture (singular) is "AFF."

2 Db13 means page 13 of Defendant's brief.

3 Pharmacovigilance is the surveillance of spontaneous reporting system ("SRS") databases "for the early detection of drug hazards that are novel by virtue of their clinical nature, severity, and/or frequency." *Id.* at ¶ 7.

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